Effective DDT Analogues with Altered Aliphatic Moieties. Isobutanes and Chloropropanes

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Several series of novel DDT analogues with altered aliphatic moieties were synthesized: isobutanes, 2-chloropropanes, 2,2-dichloropropanes, dichloroethanes, as well as other alkane and haloalkane analogues. The ratio of mouse LD_{50} to housefly LD_{50} was poorest for trichloroethane and dichloroethane compounds when the aromatic substitution was diethoxy or ethoxy-propoxy. Replacement of aliphatic chlorine atoms with methyl groups yielded safer compounds that retained good insecticidal activity. Insect toxicities were determined for susceptible and resistant strains of *Musca domestica*, for the black blowfly *Phormia regina*, and for the larvae and adults of *Culex fatigans* and *Anopheles albimanus*. Structure–activity studies indicate that steric factors are extremely important to the toxicity of DDT-type molecules. Insect toxicity was plotted against van der Waals volumes (V_w) for seven series of compounds, revealing a sharply defined minimum volume required, with a gradual loss of toxicity as larger substituents were employed. Steric interaction is apparent between the aliphatic and aromatic substituents, indicating that the molecule may fit into a tridirectional elastic sac to induce toxicity.

The simplicity of the DDT molecule and its mystical insecticidal potency have stimulated many researchers to investigate analogues which might represent improvements in the properties of the parent molecule. Some analogues have been found that are more toxic than DDT to various insects (Holan, 1969; Metcalf et al., 1971), while others have proved to be less acutely toxic to mammals (Von Oettingen and Sharpless, 1946, Metcalf et al., 1971; Holan, 1971). Detailed studies of the environmental fate of DDT and some of its analogues in a laboratory model ecosystem (Kapoor et al., 1970, 1972, 1973; Hirwe et al., 1972; and Coats et al., 1974) have demonstrated that there are insecticidally effective DDT analogues which are biodegradable and do not concentrate to high levels through food chains.

Investigations of isosteric analogues of DDT, produced largely by replacing some or all of the chlorine atoms (van der Waals radius 1.8 Å) with methyl groups (radius 2.0 Å) have confirmed the physical nature of the interaction of DDT with a receptor site in the nerve axon (Rogers et al., 1953; Stringer et al., 1955). It is evident as shown in Table I that successive replacement of the five Cl atoms of the DDT molecule with CH_3 groups produces a variety of active insecticides and that the toxicity to the housefly for these methyl isosteres can be greatly enhanced by synergism with piperonyl butoxide. This synergist is well known as a specific inhibitor of the mixed function oxidase (MFO) enzymes, and the synergistic ratio (SR), or LD_{50} alone/LD_{50} with piperonyl butoxide (P.B.), demonstrates the effect of the CH_3 groups on the biodegradability of the molecule.

Examination of Table I reveals that increasing the number of methyl groups effects a corresponding increase in the LD_{50} to the housefly; the resultant equation is $y = -267 + 246x$, with $r = 0.83$ and $F = 15.3$. Use of the synergist P.B. produces LD_{50}'s that only slightly increase as the number of methyls increases. (The exception is VIII, ditolyl-2-chloroisobutane; degradation studies in progress show this aliphatic moiety to be quite unstable.)

Within the pairs of compounds in Table I sharing the same number of total methyl groups, i.e., II vs. III, IV vs. V, VI vs. VII, it is noted that the synergistic ratio is higher in each case for the analogue with more aromatic methyls. This trend suggests that aromatic methyl groups are more susceptible to attack by housefly MFO than are aliphatic methyls.

Clearly all DDT isosteres are not equally effective insecticides, and other structurally related compounds such as Prolan or 1,1-bis(*p*-chlorophenyl)-2-nitropropane and Perthane or 1,1-bis(*p*-ethylphenyl)-2,2-dichloroethane possess effective insecticidal activity but are not strict isosteres although the general size and shape of both molecules resemble that of DDT.

In this paper we report the design of new types of DDT molecules in which we have incorporated variations in the aliphatic moiety, i.e., the CCl_3 group, in combination with the aromatic substituents which were previously determined to optimize both insect toxicity (Metcalf et al., 1971) and biodegradability (Kapoor et al., 1973). In particular, the aliphatic moiety has been varied to achieve maximal insecticidal activity, minimal toxicity to mice and fish, and a favorable rate of degradation in the environment.

MATERIALS AND METHODS

Chemical Synthesis. The compounds evaluated were all highly purified chemicals synthesized by variations of the Baeyer condensation or Friedel-Crafts alkylation reactions. Three general methods of synthesis were used for the novel compounds listed in Table II: (A) condensation of 2 mol of a substituted benzene with 1 mol of an aliphatic aldehyde in excess cold acid mixture (composition varied from 50% glacial acetic:50% concentrated H_2SO_4 to 100% concentrated H_2SO_4) to form the symmetrical 1,1-diphenylalkane; (B) condensation of 1 mol each of two different substituted benzenes with 1 mol of an aliphatic aldehyde in five volumes of the aforementioned acid mixture to form as the major product an asymmetrical 1,1-diphenylalkane; (C) condensation of a para-substituted phenyl alkyl carbinol with a substituted benzene using 1 mol of anhydrous $AlCl_3$ in ethanol-free chloroform to yield an asymmetrical 1,1-diphenylalkane.

Silica gel–hexane column chromatography was often required to obtain the desired product with a purity of at

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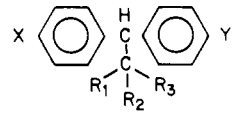
Table I. Toxicity of Some DDT Isosteres to the Housefly



No.	X	Y	R_1	R_2	R_3	Total CH_3	*Musca domestica* (♀) LD_{50}, μg/g: Alone	With P.B.	SR[a]
I	Cl	Cl	Cl	Cl	Cl	0	14	5.5	2.5
II	Cl	Cl	Cl	Cl	CH_3	1	47	17.5	2.7
III	Cl	CH_3	Cl	Cl	Cl	1	62.5	6.5	9.6
IV	Cl	Cl	Cl	CH_3	CH_3	2	55	29	1.9
V	CH_3	CH_3	Cl	Cl	Cl	2	100	17.5	5.7
VI	Cl	Cl	CH_3	CH_3	CH_3	3	85	15.5	5.5
VII	CH_3	CH_3	Cl	Cl	CH_3	3	145	18	8.1
VIII	CH_3	CH_3	Cl	CH_3	CH_3	4	>1000	>1000	
IX	CH_3	CH_3	CH_3	CH_3	CH_3	5	1250	37.5	33

[a] SR = synergistic ratio.

least 98%. Ethanol was used for crystallization of the solids. All melting points are uncorrected. NMR spectrometry and infrared spectroscopy were utilized to confirm the structures.

The following methods were used to prepare the aliphatic aldehydes not commercially available: (1) α-Chloropropionaldehyde was prepared by the method of Dick (1962), bubbling Cl_2 through propionaldehyde in 6 N aqueous HCl solutions at 10 to 15 °C and distilled three times onto molecular sieve drying agent at a final bp of 86 °C. (2) α,α-Dichloropropionaldehyde was also prepared by the method of Dick (1962) by bubbling Cl_2 through α-chloropropionaldehyde in 10 N aqueous HCl solution at 30–32 °C. The final bp was 86 °C. (3) Dichloroacetaldehyde, diethylacetal, was prepared by the method of Fritsch (1894) by bubbling Cl_2 through absolute ethanol at 25–30 °C until no more chlorine was absorbed by the stirring mixture. The product boiled at 63–64 °C at 0.38 mm pressure. (4) 2-Chloroisobutyraldehyde was synthesized by chlorination of isobutyraldehyde, using sulfuryl chloride; the method of Stevens and Gillis (1957) was used. The product distilled at 84–89 °C at 760 mm. (5) 2-Chlorobutyraldehyde was prepared by the method of Guinot and Tabuteau (1950) to a bp of 105–110 °C (lit. 107 °C).

The following types of carbinols were synthesized as precursors for use in synthesizing certain of the insecticides, in each case by condensation of the carbinol with a substituted benzene. Aluminum chloride, concentrated sulfuric acid, or concentrated sulfuric/glacial acetic acids were used as the condensing agents. (6) *p*-Methylphenyl isopropyl carbinol was synthesized from the Grignard reagent isopropyl magnesium bromide and *p*-tolualdehyde in anhydrous diethyl ether. The product was purified by vacuum distillation, boiling at 121 °C at 2.5 mm. The compound was a semiviscous liquid. (7) *p*-Methylphenyl α-chloroethyl carbinol was synthesized by reacting Grignard reagent formed by *p*-bromotoluene and magnesium turnings with α-chloropropionaldehyde. This carbinol distilled at 108–110 °C at 0.6 mm to a semiviscous liquid.

A few of the DDT analogues examined have been reported previously but with limited toxicity data: A-I, E-I, and E-II by Skerrett and Woodcock (1950); A-II and A-III, F-I, II, III by Rogers et al. (1953); C-I by Cristol et al. (1945); C-II by Riemschneider and Otto (1954); C-III and C-V by Wiechell (1894); F-IV by Holan (1971); G-I, II by Müller (1949); I-II, III K-I, II, and L-I by Harris and Frankforter (1926). Synthesis of these compounds followed the methods of those authors.

Compounds I-I, K-III, and IV were synthesized by Dr. John Williams; J-I, II, and III were synthesized by Dr. Asha Hirwe.

Table II lists the novel compounds with their melting points, method of synthesis, and toxicological data.

A generalized NMR spectrum is described for each series of compounds in Table II with an altered aliphatic moiety, utilizing NMR data for all novel compounds in each series. The ranges reported encompass the extremes for a signal among the given series of analogues (S, singlet; D, doublet; T, triplet; Qn, quintet; M, multiplet).

Isobutanes (series A): α-H at δ 3.13–3.95 (D), β-H at 1.95–2.73 (M), γ-CH_3 at 0.78–0.92 (D). Chloropropanes (series B): α-H at δ 3.75–4.05 (D), β-H at 4.45–4.88 (M), γ-CH_3 at 1.22–1.52 (D or 2D). Dichloroethanes (series C): α-H at δ 4.29–4.44 (D), β-H at 6.07–6.25 (D). Dichloropropanes (series D): α-H at δ 4.33–4.51 (S), γ-CH_3 at 2.08–2.17 (S). Chloroisobutanes (series E): α-H at δ 3.83–3.94 (S), γ-CH_3 at 1.53–1.58 (S). Neopentanes (series F): α-H at δ 3.48–3.53 (S), γ-CH_3 at 0.96–0.97 (S). Chloroethanes (series G): α-H at δ 4.14 (M), β-H at 3.85 (M) as an AB_2 system. Propanes (series H): α-H at δ 3.40–3.73 (T), β-H at 1.72–2.22 (Qn), γ-CH_3 at 0.73–0.99 (T). Bromoethanes (series I): α-H at δ 4.14–4.25 (M), β-H at 3.74–3.83 (M) as an AB_2 system. Bromopropanes (series J): α-H at δ 3.94–4.17 (D), β-H at 4.52–5.03 (M), γ-CH_3 at 1.50–1.71 (D or 2D). Dibromoethanes (series K): α-H at δ 4.37–4.52 (D), β-H at 5.99–6.20 (D). Methylbutane (series M): α-H at δ 3.28–3.45 (D), β-H at 1.83–2.50 (M). Methylpentanes (series N): α-H at δ 3.24–3.42 (D), α-H at 1.80–2,50 (M), γ-, δ-, ε-CH_x at 0.70–1.68 (M). Ethylbutanes (series O): α-H at δ 3.43–3.63 (D), β-H at 1.73–2.27 (M), γ-CH_2 at 1.05–1.58 (M), δ-CH_3 at 0.67–0.90 (T). Chlorobutane (series P): α-H at δ 3.83–4.00 (D), β-H at 4.22–4.57 (M), γ-CH_2 at 1.50–1.83 (M), δ-CH_3 at 0.88–1.12 (T).

Toxicological Assays. Insecticidal activities were determined by standard methods of the World Health Organization Insecticide Evaluation Program using laboratory-reared insects. Topical applications of 1-μL droplets of standard w/v acetone solutions of the compounds were made to the pronota of groups of twenty 3–4 day old female houseflies of the susceptible S_{NAIDM} and DDT and dieldrin-resistant R_{SP} strains. Adult black blowflies, *Phormia regina*, were treated similarly and mortalities were observed at 24 h. Pretreatment of both *Musca* and *Phormia* on the abdomen, for 1 h, with 50 μg of piperonyl butoxide was used to inhibit the mixed function oxidase enzymes and provided the synergized LD_{50} values. These are considered to give a much more

reliable indication of the intrinsic toxicity of the compound at the site of action (Metcalf et al., 1971). The synergistic ratio or SR is useful as a measure of the rate of detoxication of the compound by the mixed function oxidase enzymes.

The toxicity of the compounds to larvae and adults of *Culex fatigans* (*C. pipiens quinquefasciatus*) and to *Anopheles albimanus* was evaluated as described by Metcalf and Fukuto (1968).

The toxicity of the compounds to 8–10 weeks old female Swiss white mice was determined by oral administration of 5–10% w/v solutions in olive oil, using a micrometer-driven Hamilton syringe. The mice were observed for symptoms of intoxication and for mortality over a 1-week period.

RESULTS AND DISCUSSION

Insect Toxicity. Toxicity data in Table II reveal several compounds which surpass DDT's insecticidal activity to the insects studied. The isobutanes, 2-chloropropanes, and dichloroethanes are highly effective when at least one ring possesses a *p*-ethoxy group. Previous studies on these aliphatic moieties included mostly *p*-dichloro, -dimethyl, or -dimethoxy substituted analogues; their poor toxicity to insects resulted in their abandonment. However, the substitution combinations of methoxy-ethoxy, diethoxy, ethoxy-propoxy, dipropoxy, methyl-ethoxy, or ethyl-ethoxy produce toxic molecules. The *p*-chloro or methyl analogues show greater activity against mosquitoes than against flies while the dialkoxy and alkyl-alkoxy analogues possess superior overall insecticidal activity.

The dimethoxy analogues present a curious array of synergistic ratios in the susceptible housefly ranging from 5 for the neopentane to 267 for the chloropropane. Several of the dimethoxy compounds are apparently detoxified very rapidly while the corresponding methoxy-ethoxy and diethoxy analogues are metabolized more slowly. Metabolism studies on selected compounds from this paper are now in progress.

Mouse Toxicity. The development of a favorable mammalian safety ratio (MSR) should be an integral part of any insecticide design program. The comparative toxicities of some active DDT analogues to female Swiss white mice are presented in Table III.

All methyl-ethoxy and dimethoxy analogues tested were of low toxicity to the mouse. However, other combinations of aromatic substituents did provide increased mammalian toxicities, dependent on the aliphatic moiety involved.

Ethoxychlor is only a little less toxic than its dichloro analogue DDT. However 1,1-bis(*p*-ethoxyphenyl)-2,2-dichloroethane is much more toxic than its dichloro analogue DDD (also called TDE). The dichloromethyl moiety is at least as toxic to the mouse as the trichloromethyl moiety when each is used in combination with *p*-ethoxy ring substitution.

Serial replacement of the three chlorine atoms of ethoxychlor by methyl groups reduces toxicity to the mouse. Similarly, stepwise replacement of the two chlorine atoms of the ethoxy analogue of DDD by methyl groups also enhances mammalian selectivity. This pattern is consistent with earlier findings that mouse liver enzymes cannot degrade methoxychlor as rapidly as its neopentane analogue (Coats et al., 1974). The susceptibility of the aliphatic methyl group to microsomal oxidation by mammalian systems is especially important in light of the fact that ethoxychlor and all the diethoxy analogues in Table III possess approximately the same insecticidal activity.

The ethoxy-propoxy compounds are clearly more toxic to the mouse than the diethoxy analogues. This is of particular importance because the toxicity data in Table II shows these ethoxy-propoxy compounds to be less toxic to insects than their corresponding diethoxy analogues. Thus a distinct selective advantage is gained for mammalian safety by use of diethoxy analogues as opposed to ethoxy-propoxy ones.

Two possible explanations exist for the high toxicity of the ethoxy-propoxy analogues to mice: (1) the propoxy group could be more difficult for the mouse to metabolize, or (2) there may be a structural difference at the site of action such that ethoxy-propoxy analogues fit that site in the mouse nerve axon better than diethoxy analogues. From reported mouse LD_{50} values for similar DDT analogues with the trichloromethyl moiety, i.e., ethoxychlor 200–325 mg/kg, propoxychlor 250 mg/kg (Von Oettingen and Sharpless, 1946), and ethoxy-propoxychlor 75 mg/kg (Metcalf et al., 1971), the authors consider specificity at the site of action to be the more likely reason. From the ethoxy-propoxy series it is again noted that replacing aliphatic chlorines with methyl groups makes the compounds considerably safer to mice; aliphatic methyls available for oxidative metabolism apparently play an important role in making analogues safe for mice.

Fish Toxicity. Several of the DDT analogues have been screened for persistence and toxicity to the green sunfish, *Lepomis cyanellus*, at 0.1 ppm by the Illinois Natural History Survey. The results indicate that methyl-ethoxy analogues are safest, followed by dimethoxy analogues, and then diethoxy ones. Replacement of aliphatic chlorines with methyl groups decreased toxicity in the methyl-ethoxy series but had no demonstratable effect in the other series (Metcalf et al., 1974).

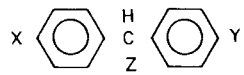
STRUCTURE–ACTIVITY RELATIONSHIPS OF DDT-LIKE COMPOUNDS

The mode of action of DDT has remained an intriguing mystery ever since the discovery of its insecticidal properties by Paul Müller in 1939. Many hypotheses have been devised and most have been disproved, till at present two major ideas prevail. The Mullins hypothesis (1955) defines the site of action of the DDT molecule as the interstices of cylindrical lipoprotein strands that constitute the nerve axon. From this idea Holan (1969) has developed the "molecular wedge" theory which proposes that the DDT molecule fits into the membrane of the nerve axon in such a way that the trichloromethyl moiety props open the sodium gate, resulting in a continuous influx of Na^+ ions.

The work of Matsumura (1969) indictes that DDT inhibits the Na^+, K^+, and Mg^{2+} ATP'ases from rat brain homogenate. Desaiah et al. (1974) suggest that the mitochondrial oligomycin-sensitive Mg^{2+} ATP'ase is more sensitive to DDT-type molecules than other ATP'ases.

Structure–activity studies have shed some light on the requirements for a toxic DDT-type molecule. Early studies by Müller (1946) and others determined that a high degree of lipophilicity is desirable; moieties with relatively large negative π-values (Fujita et al., 1964), such as hydroxyl, formyl, carboxyl, or amino, render a DDT-type molecule nontoxic probably due to a slow penetration rate through the cuticle or through the lipid sheath of the nerve. The question of symmetry has been resolved by Metcalf et al. (1971) who showed the *p*-methyl-*p'*-butoxy analogue of DDT to be quite active. Study of Prolan analogues has revealed that 1-(*p*-fluorophenyl)-1-(*p*-hexyloxyphenyl)-2-nitropropane is quite active; even the extremely asymmetric 1-(*p*-fluorophenyl)-1-(*p*-octyloxyphenyl)-2-

Table II. Effects of Various Alterations of Aliphatic and Aromatic Substituents on Insect Toxicity of the DDT-Type Molecule



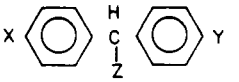
No.	Z	X	Y	*Musca domestica* NAIDM (♀) LD_{50}, μg/g Alone	*Musca domestica* NAIDM (♀) LD_{50}, μg/g With P.B.	*Musca domestica* R_{SP} (♀) LD_{50}, μg/g Alone	*Musca domestica* R_{SP} (♀) LD_{50}, μg/g With P.B.	*Phormia regina* adults LD_{50}, μg/g Alone	*Phormia regina* adults LD_{50}, μg/g With P.B.	*Culex fatigans* LC_{50} (ppm) Larvae	*Culex fatigans* LC_{50} (μg/cm²) Adults	*Anopheles albimanus* LC_{50} (ppm) Larvae	*Anopheles albimanus* LC_{50} (μg/cm²) Adults	Synthetic method	Mp, °C
A-I[a]	$CH(CH_3)_2$	Cl	Cl	>500	500	>500	>500	>250	>250	2.8	160	12	50		
A-II[a]		CH_3	CH_3	>500	310	>500	>500	>250	>250	0.85	16	>1	15		
A-III[a]		OCH_3	OCH_3	480	36	>500	120	122.5	95	0.48	>160	>1	27		
A-IV		OC_2H_5	OC_2H_5	21.5	3.5	38	12.5	14.5	6.7	0.08	14.3	0.028	9.5	A	65
A-V		OC_3H_7	OC_3H_7	100	21.5	185	185	155	140	0.30	>160	0.25	>160	A	17
A-VI		OC_4H_9	OC_4H_9	>500	>500	>500	>500	>250	>250	100	>160	>100	>160	A	
A-VII		OCH_3	OC_2H_5	65	12	110	17.5	28.75	13	0.13	16.5	0.17	6.3	B	38
A-VIII		OCH_3	OC_3H_7	120	28	235	140	157.5	135	0.25	>160	0.34	>160	B	33
A-IX		OCH_3	OC_4H_9	240	160	>500	260	>250	>250	1.5	>160	0.3	>160	B	
A-X		OC_2H_5	OC_3H_7	21	6.5	42	22.5	60	26	0.39	>160	0.056	35	B	
A-XI		OC_2H_5	OC_4H_9	90	65	180	130	>250	>250	0.24	>160	0.09	>160	B	
A-XII		OC_3H_7	OC_4H_9	>500	400	>500	>500	>250	>250	12	>160	3.5	>160	B	
A-XIII		CH_3	OCH_3	>500	175	>500	>500	>250	>250	1.4	>160	3.5	160	C	
A-XIV		CH_3	OC_2H_5	70	18	150	31	35	24	0.051	5	0.275	5	C	
A-XV		CH_3	OC_3H_7	175	100	370	220	>250	>250	0.54	>160	0.42	29	C	
X-XVI		CH_3	OC_4H_9	>500	240	>500	>500	>250	>250	1.1	>160	0.19	>160	C	
A-XVII		C_2H_5	OC_2H_5	35	22.5	85	33	55	47.5	0.064	10	0.19	4.4	C	
B-I	$CHClCH_3$	Cl	Cl	180	37	250	225	>250	107.5	0.10	17	0.064	11.7	A	71-73
B-II		CH_3	CH_3	500	24.5	>500	140	>250	125	0.22	9.7	3.5	6.9	A	
B-III		C_2H_5	C_2H_5	20	3.25	30	11.5	75	70	0.042	12.7	0.055	8	A	
B-IV		C_3H_7	C_3H_7	55	45	120	90	255	250	0.145	>160	0.068	17	A	
B-V		OCH_3	OCH_3	935	3.5	>500	41	>250	40	0.18	>160	0.21	63	A	78
B-VI		OC_2H_5	OC_2H_5	9.5	2.0	18	4.9	4.62	4.62	0.054	56	0.047	7.9	A	47-48
B-VII		OC_3H_7	OC_3H_7	28	10	85	42	42.5	22.5	0.12	>160	0.16	>160	A	19
B-VIII		OC_4H_9	OC_4H_9	445	90	500	220	>250	>250	4.2	>160	3.8	>160	A	
B-IX		OCH_3	OC_2H_5	47	4.7	100	4.8	12	12.5	0.15	>160	0.15	27	B	38
B-X		OC_2H_5	OC_3H_7	15.5	3.2	25	5.5	62.5	19.5	0.05	>160	0.075	14.5	B	
B-XI		CH_3	OCH_3	320	38.5	>500	85	97.5	10	0.165	52	0.43	13	C	
B-XII		CH_3	OC_2H_5	39	10	95	14	6.75	5.75	0.08	10	0.09	1.1	C	36-38
B-XIII		CH_3	C_3H_7	65	29	155	85	97.5	62.5	0.18	12	0.18	7.2	B	
B-XIV		$C(CH_3)_3$	OC_2H_5	>500	>500	>500	>500	>250	>250	0.08	>160	2.5	>160	B	
C-I[a]	$CHCl_2$	Cl	Cl	72.5	35	>500	>500	15.25	9	0.038	>16	0.01	1.4		
C-II[a]		CH_3	CH_3	120	11.5	225	26	10.7	8.5	0.025	5.5	0.156	2.2		
C-III[a]		OCH_3	OCH_3	850	10	>500	21.5	250	7.5	0.037	>160	0.088	16		
C-IV[a]		OC_2H_5	OC_2H_5	9	2.15	22	3.6	3.75	2.75	0.033	>160	0.02	1.6		
C-V		OC_3H_7	OC_3H_7	55	13.5	170	41	47.5	32.5	0.21	>160	0.074	>160	A	
C-VI		OC_4H_9	OC_4H_9	305	100	500	185	>250	>250	1.25	>160	0.45	>160	A	
C-VII		OC_5H_{11}	OC_5H_{11}	>500	>500	>500	>500	>250	>250	>10	>160	>10	>160	A	45-47
C-VIII		OCH_3	OC_2H_5	50	11	72.5	10.5	8.5	6.75	0.035	32.5	0.07	6	B	56-58
C-IX		OC_2H_5	OC_3H_7	16.5	8.0	36	18	20.5	12.5	0.029	125	0.031	37	B	
C-X		CH_3	OC_2H_5	39	10	65	21.5	85	7.25	0.62	9.4	1.0	1.1	B	
D-I	CCl_2CH_3	Cl	Cl	47	17.5	65	42	7.25	3.75	0.023	52	0.0084	1.1	A	75-77
D-II		CH_3	CH_3	145	18	270	7	8	7.25	0.20	8.0	0.13	5	A	74-77
D-III		OCH_3	OCH_3	65	8	155	9.5	13.5	7.25	0.061	>160	0.18	1.63	A	70

Table II (*Continued*)

D-IV		OC_2H_5	OC_2H_5	17.5	7	90	23.5	24	18	0.094	>160	0.041	49	A	84-85
D-V		OC_3H_7	OC_3H_7	>500	90	>500	115	>250	>250	0.80	>160	3.4	>160	A	
D-VI		OCH_3	OC_2H_5	110	14	140	25	12.2	11.7	0.068	8	0.076	5	B	69-70
D-VII		OC_2H_5	OC_3H_7	155	82	180	90	77.5	62.5	0.086	>160	0.16	>160	B	
E-I[a]	$CCl(CH_3)_2$	Cl	Cl	55	29	60	45	35	27.5	0.3	30	1.8	56		
E-II[a]		CH_3	CH_3	>500	>500			>250	>250						
E-III		OCH_3	OCH_3	>500	12	>500	26	75	2	>1	>160	>1	16	A	95
E-IV		OC_2H_5	OC_2H_5	115	12	180	25.5	>250	13.2	>1	>160	>1	>160	A	94
E-V		OC_3H_7	OC_3H_7	>500	240	>500	>500	>250	>250	4.2		50		A	
E-VI		OCH_3	OC_2H_5	400	30	>500	55	>250	155	5.1	75	11	34	B	83-84
F-I[a]	$C(CH_3)_3$	Cl	Cl	85	15.5	240	105	70	55	0.39					
F-II[a]		CH_3	CH_3	1250	37.5			>250	>250	>1		>1			
F-III[a]		OCH_3	OCH_3	95	19	62.5	12	17.5	5.75	0.36	>22	0.85	4.5		
F-IV[a]		OC_2H_5	OC_2H_5	37.5	9	40	18	100	92.5	0.267	>16	0.035	1.2		
F-V		OC_3H_7	OC_3H_7	>500	>500	>500	>500	>250	>250	0.6	>160	>10	>160	A	
F-VI		OCH_3	OC_2H_5	38.5	14.5	70	47	65	37.5	0.19	65	0.15	21	B	36
F-VII		OC_2H_5	OC_3H_7	240	130	310	190	>250	>250	0.35	>160	0.29	>160	B	
G-I[a]	CH_2Cl	CH_3	CH_3	>500	>500	>500	>500	>250	>250	4.1	>160	2.1	>160		
G-II[a]		OCH_3	OCH_3	>500	>500	>500	>500	>250	>250	3.5	>160	>10	>160		
G-III		OC_2H_5	OC_2H_5	>500	>500	>500	>500	>250	>250	>10	>160	>10	>160	A	48-50
G-IV		OC_3H_7	OC_3H_7	>500	>500	>500	>500	>250	>250	>10	>160	>10	>160	A	
H-I	CH_2CH_3	OCH_3	OCH_3	>500	>500	>500	>500	>250	>250	0.35	>160	19	>160	A	
H-II		OC_2H_5	OC_2H_5	>500	>500	>500	>500	>250	>250	5	>160	4	>160	A	28
H-III		OC_3H_7	OC_3H_7	>500	390	>500	>500	>250	>250	>10	>160	>10	>160	A	28
I-I	CH_2Br	CH_3	CH_3	>500	>500	>500	>500	>250	>250	5.5	>160	30	>160	A	
I-II		OCH_3	OCH_3	>500	>500	>500	>500	>250	>250	6.6	>160	>10	>160	A	
I-III		OC_2H_5	OC_2H_5	>500	460	>500	>500	>250	>250	3	>160	>10	>160	A	43-44
J-I	$CHBrCH_3$	Cl	Cl	>500	500	>500	500	>250	>250	0.075	>160	0.5	>160	A	65-67
J-II		OCH_3	OCH_3	>500	500	>500	>500	75	75	0.93	>160	>1	22	A	72
J-III		OC_2H_5	OC_2H_5	37	10	185	60	45	4	0.058	4.3	0.063	3.7	A	50
K-I[a]	$CHBr_2$	OCH_3	OCH_3	>500	>500	>500	>500	90	47.5	0.175	>160	5	160		
K-II[a]		OC_2H_5	OC_2H_5	150	110	>500	500	7.25	3.5	0.038	>160	0.048	3.9		
K-III		OC_3H_7	OC_3H_7	65	15.5	>500	27.5	70	26.25	0.083	>160	0.175	11	A	62
K-IV		OC_4H_9	OC_4H_9	>500	>500	>500	>500	>250	>250	>10	>160	>10	>160	A	
L-I[a]	CBr_3	OC_2H_5	OC_2H_5	>500	>500	>500	>500	>250	200	1.5	>160	3	>160		
M-I	$CH(CH_3)C_2H_5$	OC_2H_5	OC_2H_5	67.5	42	170	120	>250	91.25	0.125	>160	0.09	70	C	
N-I	$CH(CH_3)C_3H_7$	OCH_3	OCH_3	>500	>500	>500	>500	>250	>250	>10	>160	>10	>160	A	
N-II		OC_2H_5	OC_2H_5	>500	>500	>500	>500	>250	>250	2	>160	>10	>160	A	
O-I	$CH(C_2H_5)_2$	OCH_3	OCH_3	>500	>500	>500	>500	>250	>250	>10	>160	>10	>160	A	
O-II		OC_2H_5	OC_2H_5	150	85	>500	200	>250	>250	0.55	>160	>1	>160	A	44
P-I	$CHClC_2H_5$	OC_2H_5	OC_2H_5	23	16.3	45	20.5	45	15	0.038	>160	0.074	36	A	35-36
DDT[a]	CCl_3	Cl	Cl	14	5.5	170	40	11.5	8.25	0.07	6.9	0.015	0.23		

[a] Not a novel analogue: see methods and materials.

Table III. Toxicity of DDT Analogues to Female Swiss White Mice



Z	Acute LD_{50} (oral), mg/kg				
	X = CH_3, Y = OC_2H_5	X = Y = OCH_3	X = Y = OC_2H_5	X = OC_2H_5, Y = OC_3H_7	X = Y = Cl
CCl_3	>1000[a]	1000	200[b]-325[a]	75[a]	200[a] (DDT)
Cl_2CH_3		>1000	750	500	
$CCl(CH_3)_2$		>1000	>1000		
$C(CH_3)_3$		>1000	>1000	900	>1000
$HCCl_2$		>1000	200	200	>1000 (DDD)
$HCClCH_3$	>1000	>1000	1000	>1000	>1000
$HC(CH_3)_2$	>1000	>1000	>2100	>1000	>1000
$HCNO_2CH_3$	>1000	>1000	>1000	300	>1000[c] (Prolan)

[a] Metcalf et al. (1971). [b] Von Oettingen and Sharpless (1946). [c] Hirwe et al. (1975).

nitropropane exhibits insecticidal activity (Lee et al., 1977). The most asymmetric analogue examined here is the *p*-methyl-*p'*-butoxy analogue in the isobutane series (A-XVI in Table II); it is somewhat toxic to houseflies and *Anopheles albimanus* larvae.

A number of physicochemical parameters have been examined as to their role in imparting toxicity to a DDT analogue. Holan and Spurling (1974) have reported that distribution of charge on the molecule determines its insecticidal activity. Fahmy et al. (1973) concluded that the steric substituent constant, E_s, is the most important parameter for correlation of toxicity with structure.

Comparison of analogues with altered aliphatic moieties to the analogues in the -CCl_3 series of Metcalf et al. (1971) suggests that steric factors are indeed vitally important to the toxicity of the DDT-type compound. Whereas dipropoxy DDT is considerably less toxic than ethoxychlor and dibutoxy DDT is inactive, the ethoxy-propoxy, dipropoxy, and dibutoxy analogues in series A, B, and C (isobutanes, 2-chloropropanes, and dichloroethanes) possess good activity against most species tested (Table II).

To evaluate the steric effects of different aliphatic moieties, as well as that of aromatic substituents, an estimation of bulk is required. The steric substituent constant, E_s, used by Fahmy et al. (1973), was originally considered but was abandoned because many key values are missing in the literature. The values of Bondi (1964) for van der Waals volumes (V_w) were employed to calculate relative bulk for different groups. Correlation of E_s values (Taft, 1956) with van der Waals volumes, V_w (calculated according to Bondi) for the 20 groups from this paper for which E_s values exist, yielded $r = 0.80$ with an F ratio of 29. Calculated E_s values of Fahmy et al. (1973) correlated with V_w for the 10 groups in common at $r = 0.84$ and $F = 21$. Both are significant at $P < 0.01$, and the authors consider E_s and V_w to be closely related steric parameters, each providing a satisfactory estimate of bulk for a moiety. By holding one portion of the molecule constant while varying the other substituents, we observed the effects of volume on toxicity to the housefly.

Aromatic Substituents Held Constant. *Ethoxy Series.* The *p,p'*-diethoxy arrangement is considered to be optimal for toxicity (Holan and Spurling, 1974). In combination with 21 aliphatic moieties (alkanes, haloalkanes, and nitroalkanes) it provided a wide range of housefly LD_{50} values. Figure 1 illustrates the dependence of toxicity on aliphatic volume for diethoxy analogues. (The dotted lines in all figures are the authors' interpretations of the observed trends.) A sharply defined lower limit can be observed for an aliphatic volume necessary

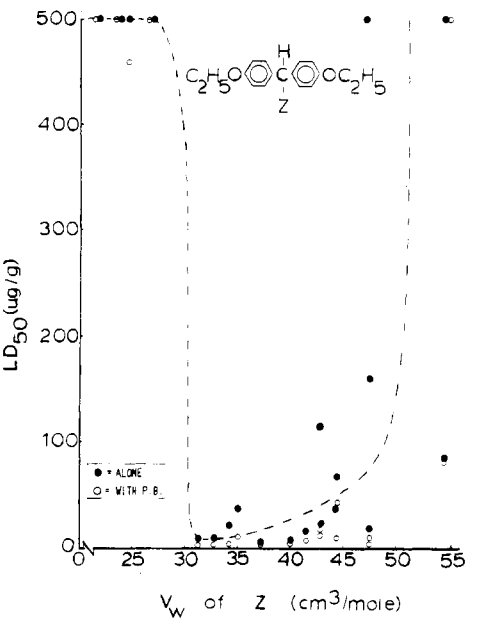


Figure 1. Relation of van der Waals volume of the aliphatic moiety Z to toxicity in the housefly *M. domestica* (N.A.I.D.M. strain).

for good toxicity. A very gradual decrease in toxicity results from increases in the volume, to a point, beyond which a sharp decline in toxicity occurs. An effective aliphatic volume of 31 to 47 cm^3/mol is defined by the plots of the diethoxy analogues.

Propoxy Series. Figure 2 demonstrates a substantially narrower range of aliphatic volumes allowable for a toxic molecule. The optimum volume appears to be 31–40 cm^3/mol, coinciding with the diethoxy curve for smaller volumes but reacting quite differently for bulkier aliphatic moieties. The longer propoxy chains do not tolerate aliphatic moieties of large volume as readily as ethoxy groups do.

Chloro Series. Using a number of toxicity values of Metcalf and Fukuto (1968) in addition to the compounds in Table II, a plot was made for *p,p'*-dichloro analogues as shown by Figure 3. The optimal aliphatic volume can be determined to be around 37–47 cm^3/mol, appearing to be narrow like the dipropoxy plots but with a distinctly larger aliphatic volume necessary for the best toxicity. The relatively small chloro substituents on the ring thus do not impart toxicity to molecules having a Z group of reduced volume.

Aliphatic Moiety Held Constant. Fahmy et al. (1973) showed toxicity to be related to the steric substituent

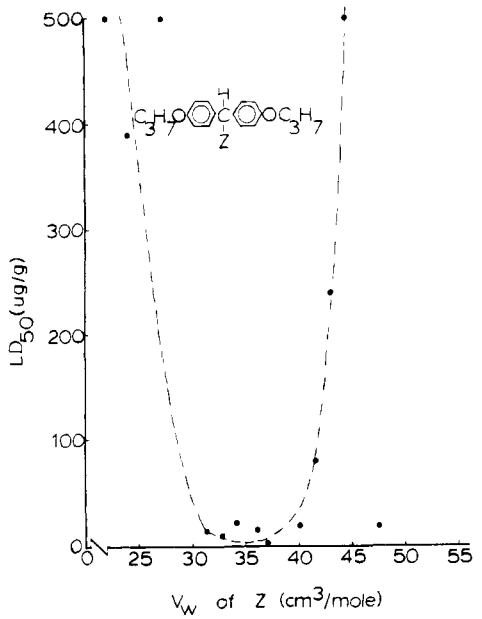


Figure 2. Relation of van der Waals volume to the aliphatic moiety Z to toxicity in the housefly *M. domestica* (N.A.I.D.M. strain).

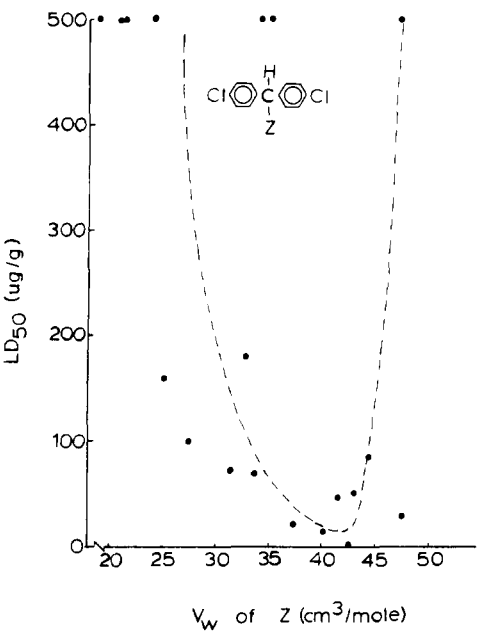


Figure 3. Relation of van der Waals volume of the aliphatic moiety Z to toxicity in the housefly *M. domestica* (N.A.I.D.M. strain).

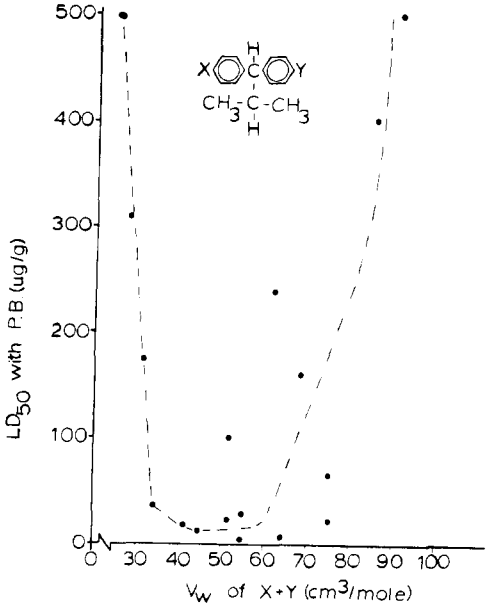


Figure 4. Relation of the combined van der Waals volumes of the aromatic substituents X and Y to toxicity in the housefly *M. domestica* (N.A.I.D.M. strain).

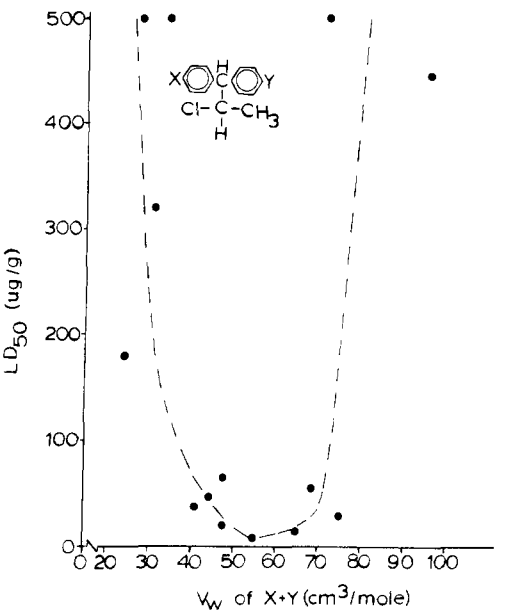


Figure 5. Relation of the combined van der Waals volumes of the aromatic substituents X and Y to toxicity in the housefly *M. domestica* (N.A.I.D.M. strain).

constant, E_s, for a series of *p*-X-phenyl-*p'*-Y-phenyltrichloroethane compounds.

The toxicities of analogues are here determined to be related to the sum of the van der Waals volumes of the two aromatic substituents when the para and para' groups are halogen, *n*-alkyl, or *n*-alkoxy.

Isobutane Series. The plot in Figure 4 shows a rather steep drop to a region of optimal volume, followed by a more gradual ascent from that region. The optimum sum of van der Waals volumes for X and Y is 40 to 65 cm^3/mol.

Chloropropane Series. Figure 5 shows a relationship for the unsynergized data similar to that described for the isobutane series. When synergized, the series of compounds presents a toxicity optimum from 35 to 65 cm^3/mol.

Dichloroethane Series. Series C in Table II possesses good insecticidal activity over a broad range of aromatic substituents, although detoxication is quite rapid, in houseflies, for the dimethyl and dimethoxy analogues. Nearly all the compounds are good larvacides. Note the significant toxicity of the dipropoxy and dibutoxy analogues.

Dichloropropane, 2-Chloroisobutane, and Neopentane Series. These classes of compounds (series D, E, and F in Table II) are, in general, less acutely toxic than the isobutane, chloropropane, dichloroethane, trichloroethane (Metcalf et al., 1971), or Prolan (Lee et al., 1977) series, all of which have a smaller aliphatic moiety than series D, E, or F. In particular, the D, E, and F series show very poor activity when the aromatic substituents are any longer than diethoxy; for smaller aromatic substituents (Cl, CH_3, CH_3O), these series sometimes show better toxicity than the corresponding analogues in series A, B, and C. The entire 2-chloroisobutane series produces unexpectedly

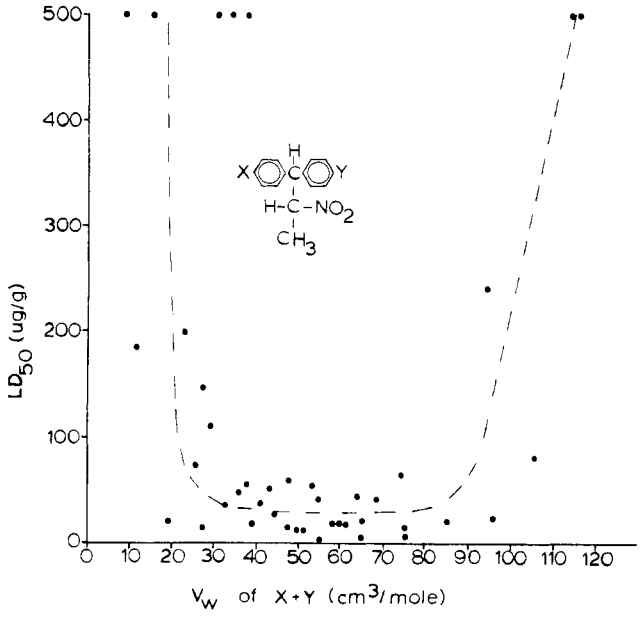


Figure 6. Relation of the combined van der Waals volumes of the aromatic substituents X and Y to toxicity in the housefly *M. domestica* (N.A.I.D.M. strain).

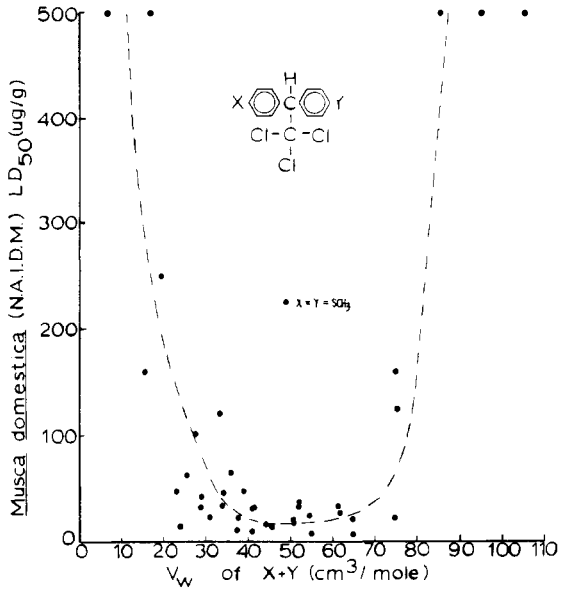


Figure 7. Relation of the combined van der Waals volumes of the aromatic substituents X and Y to toxicity in the housefly *M. domestica* (N.A.I.D.M. strain).

inferior toxicity values considering the similarity of the series to the trichloroethanes, dichloropropanes, and neopentanes. The compounds in series E dehydrochlorinate rapidly in solution, on silica gel, and probably in insects; this is apparently attributable to the inherent instability of the tertiary chloride.

Series G, H, and I have too small an aliphatic moiety, while series L, N, and O have too large an aliphatic moiety. The bromoalkanes (I, J, K, and L) probably dehydrobrominate too readily (Berger and Young, 1962) to be good insecticides. The 2-methylbutane (M) and 2-chlorobutane (P) are fairly active as expected from their steric resemblance to Bulan.

Prolan Series. Toxicity data of Lee et al. (1977) for 42 analogues of Prolan were plotted to test the concept of optimum steric dimensions. The result is Figure 6 in which a definite optimal range can be observed; substituents used range from hydrogen and fluorine to decyloxy.

DDT Series. The data of Metcalf et al. (1971) have been used to generate Figure 7. This unsynergized plot illustrates well the concept of an optimum for the summed volumes of X and Y, with the exception of methiochlor (X = Y = SCH_3) which has been shown to be extremely susceptible to microsomal oxidative degradation (Kapoor et al., 1970).

The same basic structure–activity relationships hold true for several species other than the housefly, with some restrictions.

Black Blowfly, *Phormia regina*. When the aromatic substituents are held constant, toxicity varies with the volume of the aliphatic moiety as shown in Figure 8. When the aliphatic moiety is held constant and aromatic substituents are varied, the steric factors still prove very important but for small aliphatic moieties at least one aromatic ethoxy group is necessary, while for series D, E, and F, with larger aliphatic moieties, the dimethoxy analogues are consistently superior to ones possessing ethoxy groups. There is also a distinctly decreased tolerence in the size of aromatic substituents within any given series of compounds. The conclusion is that steric theories hold for *Phormia regina*, but that there is a less elastic receptor site than for the housefly, at least in the portions occupied by the aromatic substituents.

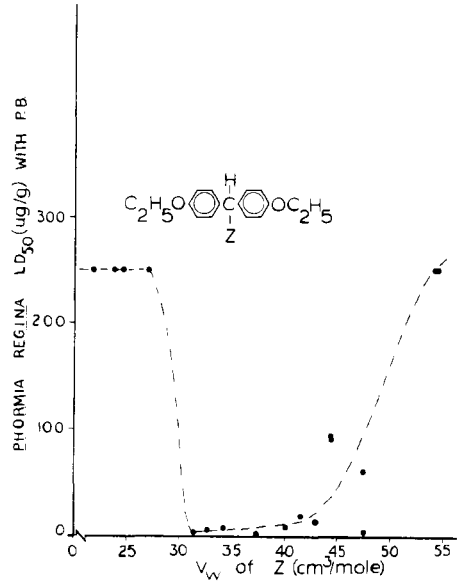


Figure 8. Relation of van der Waals volume of the aliphatic moiety Z to toxicity in the black blowfly *Phormia regina*.

Mosquitoes, *Culex fatigans* and *Anopheles albimanus*. Plotting of van der Waals volumes (V_w) vs. the larval LC_{50} values for series of compounds creates broad, shallow U-shaped curves supporting the concept of an optimum volume; however, differential solubilities in water place limitations on the accuracy of LC_{50} values for some of the less toxic analogues. For the adult *C. fatigans*, analogues with at least one aromatic chlorine or alkyl group are superior, while *A. albimanus* adults are susceptible to diethoxy analogues as well as those with aromatic chlorine or alkyl groups. Aliphatic chlorines enhance the toxicity of chloro- and alkyl-substituted analogues to *A. albimanus* adults.

Shape of the Plots. The most frequently recurring pattern is one of a steep descent to the region of very low LD_{50}'s, followed by a very gradual increase in LD_{50} values, and finally by a rapid loss of toxicity; Figure 8 is a prime example. We interpret the sharply defined minimum volume necessary for toxicity to be due to tension put on the membrane that makes up the sac or flexible cavity into

which the DDT-type molecule fits. Molecules with less than the minimum bulk requirements fit into the sac but fail to touch all sides to distort the sac slightly or create a stress on the walls of the cavity.

Through the region of optimal toxicity the slight loss of toxicity with increase in volume is probably due to the various conformations of the larger molecules getting into the sac at different rates. Since only the *p*-dichloro series (Figure 3) fails to show this property, it is assumed the alkyl and alkoxy chains on the aromatic rings are most important in providing conformational flexibility; however, some advantage is also gained with an aliphatic moiety like that of Bulan (1,1-bis(*p*-chlorophenyl)-2-nitrobutane) and its analogues, which permits considerable conformational freedom. This is evidenced by the fact that the 2-nitrobutane analogues are consistently a little more toxic than predicted by the plots presented in Figures 1, 2, 3, and 8. Perhaps an E_s value could better explain the excellent toxicities of the Bulan analogues.

With further increases in bulk, the molecule suddenly becomes too large to fit into the sac, and toxicity is lost entirely.

Regions of Optimal Activity. The width of the curves vary, with the dipropoxy (Figure 2) and dichloro (Figure 3) series having the narrowest range of optimum volumes; the series of bulky dipropoxy phenyl analogues has an optimum aliphatic volume considerably smaller than the series of dichlorophenyl compounds. The diethoxy series has the broadest range of optimum aliphatic volumes. Among the several aliphatic series plotted, the Prolan series allows the broadest range for volumes of aromatic substituents, perhaps partially due to additional conformational flexibility. The other series with disubstituted β-carbon atoms (isobutanes, 2-chloropropanes, and dichloroethanes) are more tolerant of large aromatic substituents than the $-CCl_3$ series is, but less toxic than corresponding $-CCl_3$ analogues when smaller aromatic substituents are employed (Figures 1 and 2).

These observations seem to prove the theory which Fahmy et al. presented, that the aliphatic portion of the molecule is extremely important and interacts with the aromatic substituents in a manner such that the overall size of the molecule is the most important factor for toxicity of DDT-type molecules.

Statistical Analysis. The shape of the plots, as described in the above paragraphs, is not really suggestive of a parabola; the function is not expected to be parabolic considering our arguments to explain the fit of the molecules into an elastic sac. However, it has been customary to evaluate U-shaped curves by parabolic regression and has been attempted for DDT-type compounds (Fahmy et al., 1973; Lee et al., 1977). Therefore, we have correlated toxicity with van der Waals volume for each series plotted in Figures 1–8 using the compounds for which accurate LD_{50}'s could be calculated; dibromo- and tribromoethanes were omitted because of their instability. Parabolic equations were obtained in the form of $LD_{50} = A_0 + A_1(V_w) + A_2(V_w)^2$. The three largest series are presented as examples of the degree of fit (asterisk indicates that values are significant at $P < 0.001$).

Series	Figure	N	r	r^2	F ratio
Diethoxy	1	17	0.90	0.81	30.3*
Prolan	6	35	0.63	0.40	10.6*
DDT	7	38	0.70	0.49	17.0*

To test the theory of additive volumes of aromatic and aliphatic substituents on a molecule, we attempted to correlate the total molecular volume (V_w^m) with synergized toxicity to the susceptible housefly for 176 DDT-type compounds tested in this laboratory in the last 5 years; these include the DDT analogues of Metcalf et al. (1971), Prolan analogues of Lee et al. (1977), 20 benzylaniline and 9 benzyl phenyl ether analogues of Hirwe et al. (1972), 11 Bulan and 2 isobulan analogues, as well as those presented in this paper which are di- or trisubstituted at the β carbon. The following equation was obtained: $LD_{50} = 2120 - 22.9(V_w^m) + 0.062(V_w^m)^2$. The $r = 0.40$ and $r^2 = 0.16$ which are good for 174 degrees of freedom show significance at $P < 0.01$. The analysis of variance yielded an $F = 16.3$ which indicates excellent correlation.

While the authors do not consider the relationship to be parabolic, but rather a skewed-U, the various parabolic regressions do indicate that an optimum bulk can be demonstrated for any series of analogues. The steric requirements may be within a very narrow range, e.g., dipropoxy series, or tolerant over a very broad range; the Prolan series is active over the widest range, probably because the $-NO_2$ in the aliphatic moiety can rotate freely, contributing extra steric flexibility.

Clearly, factors other than steric ones are also of importance in contributing to toxicity. For example, a comparison of aromatic substituents reveals that alkyl groups are slightly inferior to alkyloxy, alkylthio, and halogen substituents of similar volume. Perhaps the alkyl groups' lack of lone pairs of electrons reduces their affinity for the active site. Other parameters such as lipophilicity, charge distribution, and rate of metabolism may play roles as well, but steric factors seem to contribute the most among the requisite properties for a toxic DDT analogue.

CONCLUSIONS

The model of Holan, with fixed dimensions for X, Y, and Z, has been refined by exhibiting much flexibility within the molecule. The asymmetric molecules of Metcalf et al. (1971) and Lee et al. (1977) and the proven importance of E_s for aromatic substituents in imparting toxicity (Fahmy et al., 1973) have helped to elucidate the requirements for an active DDT-type molecule. Fahmy et al. state that they suspect steric interaction between the aromatic and aliphatic portions of the molecule but lack the matrix of compounds necessary to prove it. We submit that the optimum aliphatic volume is dependent on the sum of the volumes of the aromatic substituents, and that efficacies of aromatic substituents depend on the aliphatic moiety.

Plots of many aromatic series and aliphatic series reveal a distinct minimum volume necessary to induce toxicity with less distinct upper limits to molecular volume, due to conformational allowances.

Statistical evaluation of individual series and a group of 176 analogues of various types indicates that steric factors are very important in the structure–activity relationships of DDT-type compounds.

Several of the compounds in Table II, notably the isobutane A-IV and the chloropropane B-VI, show promise as practical insecticides.

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Persistence and Metabolism of Oxadiazon in Soils

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Oxadiazon [2-*tert*-butyl-4-(2,4-dichloro-5-isopropylphenyl)-Δ^2-1,3,4-oxadiazolin-5-one] was incorporated in both moist and flooded Matapeake loam and Monmouth fine sandy loam at 10 ppm plus 10 μCi [*phenyl*-^{14}C]oxadiazon. Soils were sampled after 0, 2, 4, 8, 10, and 25 weeks to determine the distribution of ^{14}C in CO_2, volatile products, soil-bound residues, and metabolites. Oxadiazon degraded slowly in all soils; after 25 weeks, 0.1–3.5% of the [^{14}C]oxadiazon was lost as CO_2, 0.5–1.1% as volatile products, and 1.9–13.3% was bound. Distribution of ^{14}C in the bound residue fraction of the moist soils was fulvic acid > humic acid or humin, whereas ^{14}C was fairly evenly distributed in the flooded bound residue fraction. Oxadiazon, a phenolic and a carboxylic acid derivative were identified in the soil extracts by TLC, GLC, and mass spectral analysis. A dealkylated derivative of oxadiazon was detected by TLC.

Oxadiazon (2-*tert*-butyl-4-(2,4-dichloro-5-isopropoxyphenyl)-Δ^2-1,3,4-oxadiazolin-5-one), Wiswesser Line-Formula Notation (T5NNVOJ BR BG DG EOY && EX), is a promising herbicide for controlling annual grasses and broadleaf weeds in rice, turf, orchards, soybeans, onions, potatoes, and ornamentals; it was originally discovered by the Societe des Usines Chimiques Rhone-Poulenc in 1969 (Burgaud et al., 1969). The adsorption, translocation, and metabolism of oxadiazon has been studied extensively in rice plants (Hirata and Ishizuka, 1975; Ishizuka et al., 1974; Ishizuka et al., 1975). Oxadiazon's major degradation products in rice were carboxylic acids, alcohols, and dealkylated derivatives. Cleavage of the oxadiazolin ring resulted in a product identified as the 1-(2,4-dichloro-5-isopropoxyphenyl)-1-methoxcarbonyl-2-trimethylacetylhydrazine in rice. However, a limited amount of work has been conducted on oxadiazon in soils. Ambrosi and Desmoras (1973) working with three different soils, showed that oxadiazon was rapidly and strongly bound to soil colloids just after treatment. Carringer et al. (1975) investigated the adsorption–desorption of oxadiazon on soil organic matter and montmorillonite clay. When six selected pesticides, including oxadiazon, were compared, their adsorption seemed to be inversely related to their water solubility, i.e., compounds with the lowest water solubility were adsorbed the most. It was postulated that compounds with low water solubility like oxadiazon were preferentially adsorbed on hydrophobic areas in soil organic matter and removed from solution.

The purpose of this study was to examine oxadiazon's persistence, binding, and metabolism in two soils under moist and flooded conditions.

METHODS AND MATERIALS

Chemicals. [*phenyl*-^{14}C]Oxadiazon, specific activities 25.8 μCi/mg, was obtained from Rhone-Poulenc, 94400 Vitry/Seine, France. Unlabeled oxadiazon (I), oxadiazon-phenol (II), oxadiazon-acid (III), and methoxy-oxadiazon (IV) were available for cochromatography and

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